PATENTS SUMMARY
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Inventor: Keiji Iguchi, et. al. Issue Date: 10/04/84
Assignee: Kanebo Food Co. Inc Date of Application:
Title:
ANTICARIES AGENT

Japan A Patent

Desc.:
Flavoring components inhibit Streptococcus Mutans. The effect is synergistically enhanced by other compounds including fatty acids and lactones. Effective compounds include: Cinnamic aldehyde, cuminaldehyde, carvone, limonene, cineol, citral, cintronellol, thymol, eugenol, terpineol and methyl salicylate. Chewing gum is mentioned as a vehicle.

Key Words:
10 CHEWING GUM
20 Anticaries/Antiplaque (Gum)
400 FLAVORS/FRAGRANCES
402 Natural
408 Cinnamon
409 Other Spice
410 Mint
411 Fruit
420 Ingredients
600 ORAL HEALTH
601 Anticaries/Antiplaque/Anticalculus
604 Dentifrice
799 Other Company/Institution
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ANTICARIES AGENT

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[54] Title: ANTICARIES AGENT

Specification

1. *Title of the Invention*

ANTICARIES AGENT

2. *Claims*

(1) An anticaries agent consisting of an effective component or components of a natural extract alone, or such component or components and at least one anticaries component selected from the group consisting of the components A, B and C below

A: synthetic flavorings

B: carboxylic acids

C: lactones.

(2) The anticaries agent as defined in claim 1, wherein the effective component or components of a natural extract are at least one of the components selected from the group consisting of hinokithiol, cinnamaldehyde, cuminaldehyde, carvone, limonene, cineole, borneol, citral, citronellal, geraniol, thymol, carvacrol, methyl chavicol, eugenol, terpineol, chavicol, methyl salicylate and di-*n*-propyl disulfide.

(3) The anticaries agent as defined in claim 1, wherein the anticaries component A, i.e., the synthetic flavoring, is at least one of the synthetic flavorings selected from the group consisting of cresyl acetate, cyclamen aldehyde, isoeugenol, methyleugenol, heliotropin, ethyl salicylate, *n*-decanal and *p*-methyl acetophenone.

(4) The anticaries agent as defined in claim 1, wherein the anticaries component B, i.e., the carboxylic acid, is at least one of the carboxylic acids selected from the group consisting of capric acid, lauric acid, myristic acid, palmitic acid, stearic acid, oleic acid, linoleic acid, rosin acid, vanillic acid, undecanoic acid, undecylenic acid and enanthoic acid.

(5) The anticaries agent as defined in claim 1, wherein the anticaries component C, i.e., the lactone, is at least one of the lactones selected from the group consisting of *d*-decalactone, *d*-dodecalactone, *d*-undecalactone, *d*-tridecalactone and *d*-tetradecalactone.

3. Detailed Description of the Invention

The present invention relates to an anticaries agent, i.e., an agent for oral use which prevents dental caries or hinders their progress. The occurrence of dental caries, i.e., cavities, has increased considerably in recent years and has actually become a social problem. On the other hand, progress is being made in the study of the cause of dental caries,and according to currently accepted theory, the disease is due to the effect of caries-causing bacteria, which convert the sucrose contained in food to glucan which is insoluble and tacky. By the effect of glucan thus formed, caries-causing bacteria adhere to the dental surface and proliferate, and as a result a dental deposit is formed. Using this dental deposit as a base, the bacteria living therein generate an acid through sugar fermentation, and the acid promotes the dental caries. Various methods can be contemplated for preventing dental caries, including a method of enhancing the resistance of the teeth, a method of excluding sucrose or using a sweetener instead of sucrose, a method of decomposing insoluble glucan formed from sucrose or blocking the formation of glucan, and a method of wiping out caries-causing bacteria. Each of these methods has its own advantages and disadvantages, but since dental caries is essentially a condition caused by contact with caries-causing bacteria, it is believed that the most effective way of preventing dental caries is to wipe out the cause, i.e., caries-causing bacteria. Such bacteria include Streptococcus Mutans and Streptococcus Sanguis. Many attempts have been made in the past to kill such caries-causing bacteria in order to prevent

dental caries. For example, the use of antibiotics such as penicillin and erythromycin, cell wall dissolving enzymes which dissolve the cell wall of caries-causing bacteria, and sterilizing agents such as cyclohexydine has been tried. However, there is a problem with the use of these substances in that they destroy the natural balance of bacteria by disturbing oral and intestinal flora and can also cause side effects. Since the problem of side effects has not been resolved, these substances have not gained widespread use. Thus, at present there is no definitive method of preventing dental caries, and no preventive method has been established which is superior to the physical method of cleaning the teeth with a toothbrush after meals.

In view of this situation, the present inventors conducted a series of studies in order to find a preventative and obtained at least a clue to one in the discovery that certain flavorings have antibacterial activity; we thereafter conducted a series of studies over a long period of time on an extremely large number of flavorings to determine if they might be usable as anticaries agents. As a result, we found that an excellent sterilization effect for caries-causing bacteria is obtained when an effective component of a natural extract (flavoring) is used separately or in a suitable combination with a flavoring substance (food flavoring) such as carboxylic acids or lactones, or a synthetic flavoring such as isoeugenol. Thus, the object of our invention is an anticaries agent consisting of an effective component or components of a natural extract alone, or such component or components and at least one anticaries component selected from the group consisting of the components A, B and C below

A: synthetic flavorings

B: carboxylic acids

C: lactones.

The most important feature of this invention is the use of flavoring components which have no side effects and are quite safe.

The present invention is described below in further detail.

There are some reports which state that certain of the effective components of natural extracts, natural substances and flavoring compounds have antibacterial activity. However, there are no reports dealing with activity directed against Mutans bacteria, the most potent caries-producing agents. Thus, as a first step, we collected effective components of natural extracts for which some kind of antibacterial activity has been reported, or which are used relatively commonly, and measured their activities against Mutans bacteria. The antibacterial activities were measured in the following manner: Each of the effective components of the natural extracts was diluted as a 5% alcohol solution (this was treated as the test component),and the latter was added to a heat infusion broth containing 5% sucrose at a proportion of 1/100-1/1000 (i.e., so that the concentration of the 5% alcohol solution, the test component, became 1/100-1/1000), and after the broth solidified, Mutans bacteria (Streptococcus Mutans RIMD 3125001) was injected into the broth with a syringe and cultured at 37°C for 72 hr or more, with the growth of bacteria on the broth surface being observed during culturing. Substances which proved active against Mutans bacteria are listed in Table 1. The presence of anti-Mutans activity is indicated when a test component was added to the broth at the proportion of 1/1000; the culturing was conducted at 37°C for more than 72 hr, and no growth of Mutans bacteria was observed. The concentration of the test component was increasingly lowered, and the inverse of the minimum concentration at which the anti-Mutans activity was observed (i.e., the effective growth-preventing concentration) is shown as the anti-Mutans activity value. Thus, for instance, if the concentration of the test component is 1/1000, the inverse of this, or 1000, is the activity

Table 1

Substance	Anti-Mutans activity
hinokithiol	10,000
cinnamic aldehyde	4,000
cuminaldehyde	2,000
carvone	1,000
limonene	1,000
cineole	1,000
borneol	1,000
citral	2,000
citronellol	4,000
citronellal	2,000
geraniol	1,000
thymol	2,000
carvacrol	2,000
methyl chavicol	1,000
eugenol	1,000
terpineol	1,000
chavicol	1,000
methyl salicylate	1,000
di-*n*-propyl disulfide	4,000
goldthread extract	1,000
magnolol	7,000
erythromycin	14,000

value. As a reference, similar experiments were conducted with goldthread, magnolol — which is an effective component of goldthread — and erythromycin, which is an antibiotic having a sterilizing effect upon Mutans bacteria. These results are also listed in Table 1. The effective components of the natural extracts listed in Table 1 have equal or better anti-Mutans activity than goldthread extract which is also known as an anticaries agent (see Japan Kokai Sho 57-85319).

In light of the fact that effective components of natural extracts exhibit a strong anti-Mutans activity, we expanded the scope of our search to synthetic flavorings and natural flavorings such as carboxylic acids and lactones, and checked their anti-Mutans activities. The results are shown in Table 2. The synthetic flavorings, carboxylic acids and lactones listed in Table 2 exhibit a very high anti-Mutan activity.

In the next step, the components listed in Table 1 and Table 2 were

mixed, and the anti-Mutans activities of the mixtures were measured. The results are shown in Table 3. As indicated, anti-Mutans activities higher than the arithmetic average of the anti-Mutans values of the components of Tables 1 and 2 were obtained. This indicates that a strong synergistic effect is obtained by mixing together a component listed in Table 1 and another component listed in Table 2. Actually, in general, it is rare that

Table 2

	Substance	Anti-Mutans activity
Synthetic flavoring	dicresyl acetate	1,000
	cyclamen aldehyde	4,000
	isoeugenol	2,000
	heliotropin	1,000
	ethyl salicylate	1,000
	n-decanal	1,000
	p-methyl acetophenone	1,000
	methyleugenol	1,000
Carboxylic acid	capric acid	2,000
	lauric acid	2,000
	myristic acid	4,000
	palmitic acid	2,000
	stearic acid	2,000
Carboxylic acid	oleic acid	1,000
	linoleic acid	1,000
	rosin acid	1,000
	vanillic acid	1,000
	undecanoic acid	1,000
	undecylenic acid	1,000
	enanthoic acid	1,000
Lactone	*d*-decalactone	1,000
	d-dodecalactone	2,000
	d-undecalactone	1,000
	d-tridecalactone	2,000
	d-tetradecalactone	2,000

only one flavoring component is used; it is more usual to mix various components together in order to obtain a composite flavoring producing a desired taste. Thus, the fact that the mixing of the components of Table 1 with those of Table 2 produces a strong synergistic effect, as shown in Table 3, is very useful

Table 3

	Substance	Anti-Mutans activity value	No. 1 (parts)	No. 2 (parts)	No. 3 (parts)	No. 4 (parts)	No. 5 (parts)
Effective component	hinokithiol	10,000	10	10	5	5	5
	cinnamaldehyde	4,000	10	10	5	20	10
	citral	2,000	50	—	—	—	20
	geraniol	1,000	—	—	—	10	—
	thymol	2,000	10	10	20	20	—
	citronellol	4,000	40	20	—	—	40
	limonene	1,000	—	20	—	—	—
	methyl chavicol	1,000	20	10	10	10	—
	carvone	1,000	10	—	10	—	10
Synth. flavor.	cyclamen aldehyde	4,000	—	20	—	—	40
	isoeugenol	2,000	—	10	—	—	—
Carboxylic acid	myristic acid	4,000	—	—	10	—	—
	lauric acid	2,000	—	—	10	—	—
	oleic acid	1,000	—	—	10	—	20
Lactone	*d*-dodecalactone	2,000	—	—	—	10	10
	d-tridodecalactone	2,000	—	—	—	10	10
	d-tetradecalactone	2,000	—	—	—	10	10
Arithmetic mean of the anti-Mutans activities			$\frac{450}{150} \times 1000$	$\frac{370}{110} \times 1000$	$\frac{200}{80} \times 1000$	$\frac{250}{95} \times 1000$	$\frac{530}{175} \times 1000$
Actual anti-Mutans activity			10,000	8,000	8,000	6,000	10,000

from a practical standpoint.

Since the anticaries agents of this invention consist of flavoring components which are actually widely used in the food industry and like industries, and which have proved quite safe, no side effects occur at all. In other words, although the anticaries activity of the agents of this invention is somewhat lower than that of erythromycin, which is an antibiotic, these agents are not antibiotics, and therefore do not have side effects such as those observed with antibiotics (e.g., disturbance of the microorganism balance in the living

body, appearance of drug-resistant bacteria, etc.), and no problems arise when they are used over a long period of time. Moreover, since the anticaries agents of this invention are chosen from a wide range of flavoring components, such as effective components of natural extracts and synthetic flavoring agents, a pleasant flavor can be produced for the item to which the anticaries agent is added by using a suitable combination of the flavoring components. This effect is extremely useful from the standpont of actual clinical use, in view of the fact that the administration of the anticaries agent extends over a fairly long period of time and that, for the purpose of preventing dental caries, the administration should preferably be started in infants at about age one, when tooth formation begins.

Moreover, since the anticaries agents of this invention can hinder the growth of Mutans bacteria at a very low concentration, a strong anticaries effect can be obtained by using a very small amount. For example, the anti-Mutans activity values of hinokithiol of Table 1, isoeugenol of Table 2 and mixture No. 5 of Table 3 are 10,000, 2,000 and 10,000, respectively, and correspond to concentrations of 5 μg/mL, 25 μg/mL and 5 μg/mL. Thus, it can be seen that an excellent anticaries effect can be obtained with only a very minute quantity.

Thus, since the anticaries agents of this invention are flavoring components and produce an excellent anticaries effect with only a small quantity, they can add flavor to mouthwash, troche, toothpaste, chewing gum and the like, while producing the same anticaries effect. Moreover, the use of the anticaries agents of this invention does not give rise to any side effects such as those observed with prior art antibiotics and can thus be used continuously over a long period of time. Moreover, although some of the anticaries agents of this invention are known to have antibacterial activity,

this activity is directed mainly against certain pathogenic bacteria, such as colitis germs or dysentery germs, and there has been no proof of any activities affecting special bacteria such as Mutans bacteria (which do not belong to any classification of chain-like bacteria, so it can be said that the anticaries agents of this invention produce excellent effects which have not been anticipated in the prior art.

This invention will be described below with reference to examples.

The examples described below use mixtures listed in Table 3 which afford an excellent synergistic effect.

Example 1

Anti-Mutans activity was measured for mixture no. 1 of Table 3, and the effective concentration for preventing the growth of Mutans bacteria was found to be 1/10,000 (anti-Mutans activity 10,000). This mixture no. 1 had a spicy citrus-like flavor, and when the 5% alcohol solution of this mixture was added to 10% sucrose solution in a proportion of 1/10,000, and the resultant solution was placed in the mouth, there was no unpleasant taste or irritation.

Example 2

Anti-Mutans activity was measured for mixture no. 2 of Table 3,and the effective concentration for preventing the growth of Mutans bacteria was found to be 1/8000 (anti-Mutans activity 8,000). This mixture had a spicy, floral, citrus-like flavor,and when the 5% alcoholic solution of this mixture was added to 10% sucrose solution in a proportion of 1/8000 and the resultant solution was placed in the mouth, there was no unpleasant taste or irritation.

Example 3

The effective concentration for preventing the growth of Mutans bacteria was measured for mixture no. 3 of Table 3 and was found to be 1/8000 (anti-Mutans activity 8000). This mixture had a spicy flavor with a strong fatty acid smell, and when a 5% alcoholic solution of this material was added to 10% sucrose solution in a proportion of 1/8000 and the resultant solution was placed in the mouth, there was no unpleasant taste or irritation.

Example 4

The effective concentration for preventing the growth of Mutans bacteria was measured for mixture no. 4 of Table 3 and was found to be 1/6000 (anti-Mutans activity 6000). This mixture had a spicy, fruity flavor, and when a 5% alcoholic solution of this material was added to 10% sucrose solution in a proportion of 1/6000 and the resultant solution was placed in the mouth, there was no unpleasant taste or irritation.

Example 5

The effective concentration for preventing the growth of Mutans bacteria was measured for mixture no. 5 of Table 3 and was found to be 1/10,000 (anti-Mutans activity 10,000). This mixture had a spicy floral flavor, and when a 5% alcoholic solution of this material was added to 10% sucrose solution in a proportion of 1/10,000 and the resultant solution was placed in the mouth, there was no unpleasant taste or irritation.

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